PCT/IN03/00219 10/517944

Rec'd PCT/PTO 13 DEC 2004

REC'D 01 OCT 2003
WIPO PCT

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application & Provisional Specification filed on 17/04/2003 in respect of Patent Application No. 387/MUM/2003 of Sun Pharmaceutical Industries Ltd, Acme Plaza Andheri-Kurla Road, Andheri (E), Mumbai-400 059, Maharashtra, India. An Indian Company.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Dated this 01 day of August 2003

M.A. Hafeez

(M.A. HAFEEZ)
ASST. CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970
(39 OF 1970)

APPLICATION FOR GRANT OF A PATENT
(See sections 5(2), 7, 54 and 135 and rule 33A)

We, SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, INDIA

AN INDIAN COMPANY

hereby declare -

(i) that we are in possession of an invention titled "**CONVENIENT SYNTHESIS OF S-FLUOROMETHYL 6α,9α-DIFLUORO-11β-HYDROXY-16α-METHYL-17α–PROPIONYLOXY-3-OXOANDROSTA-1,4-DIENE-17β–CARBOTHIOATE**"

(ii) that the provisional specification relating to this invention is filed with this application.

(iii) that there is no lawful ground of objection to the grant of a patent to us.

We, further declare that the inventors for the said invention are
1) Dr. Jadav Kanaksinh Jesingbhai 2) Dr. Chitturi Trinadha Rao 3) Dr.Thennati Rajamannar; of SUN PHARMA ADVANCED RESEARCH CENTRE, AKOTA ROAD, AKOTA, BARODA 390020, GUJARAT, INDIA; an Indian national.

We claim the priority from the applications filed in convention countries, particulars of which are as follows: Not Applicable

We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: Not Applicable

We state that the application is divided out of our application, the particular of which are given below and pray that this application deemed to have been filed under section 16 of the Act: Not Applicable

That we are the assignee of the true and first inventors.

That our address for service in India is as follows-

Dr. RATNESH SHRIVASTAVA,
INTELLECTUAL PROPERTY CELL,
SUN PHARMACEUTICAL INDUSTRIES LTD,
ACME PLAZA, ANDHERI-KURLA ROAD,
ANDHERI (E), MUMBAI-400 059, INDIA,
TELEPHONE NO-28397632, FACSIMILE NO- 28212110.

ORGN.
387/MUM/2003
17/4/2003

17/4/03

FORM 2

THE PATENTS ACT, 1970
(39 OF 1970)

PROVISIONAL SPECIFICATION
(See section 10)

CONVENIENT SYNTHESIS OF S-FLUOROMETHYL 6α,9α-DIFLUORO-11β-HYDROXY-16α-METHYL-17α–PROPIONYLOXY -3-OXOANDROSTA-1,4-DIENE-17β–CARBOTHIOATE

SUN PHARMACEUTICAL INDUSTRIES LTD.

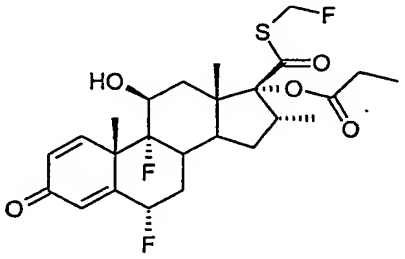
A company incorporated under the laws of India having their office at ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, MAHARASHTRA, INDIA.

The following specification describes the nature of this invention.

ORIGINAL
87/MUM/2003

PROCESS FOR THE PREPARATION OF S-FLUOROMETHYL 6α, 9α-DIFLUORO-11β-HYDROXY-16α-METHYL-17α–PROPIONYLOXY-3-OXOANDROSTA-1,4-DIENE-17β–CARBOTHIOATE

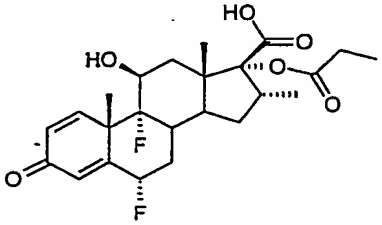
The present invention relates to the process for preparation of S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate. a compound of **formula 1**. S-fluoromethyl 6α,9α-difluoro-11 β-hydroxy-16 α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate, commonly known as fluticasone propionate (INN), is used as an anti-inflammatory and antipruritic agent.



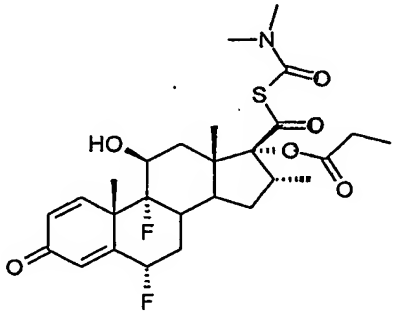
1

PRIOR ART

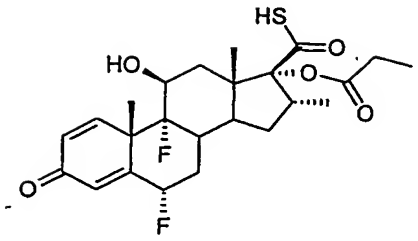
United States Patent No. 4335121 (referred to herein as the '121 patent, Indian reference not available) discloses the compound of **formula 1** and its preparation. It discloses the process of its preparation by treating a compound of **formula 2** with dimethylthiocarbamoyl chloride to yield a compound of **formula 3** ,



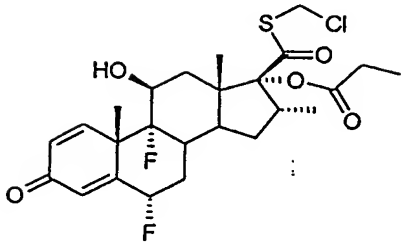
2



3



4



5

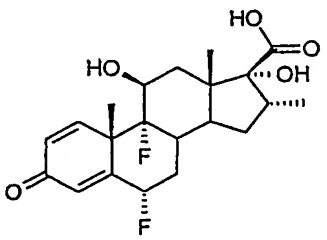
which is decomposed by refluxing in diethylamine to the thioic acid of **formula 4**. The compound of **formula 4** is then reacted with bromochloromethane in presence of sodium bicarbonate to give a chloromethyl ester of **formula 5**. The compound of **formula 5**, is converted to an iodomethyl ester by halogen exchange and subsequently treated with silver fluoride to yield the compound of **formula 1.** This process of preparation of the compound of **formula 1** is very tedious, lengthy, and involves use of expensive and sensitive chemicals, viz. silver fluoride. This prior art teaches the use of ammonia, a primary amine or more preferably a secondary amine such as diethylamine or pyrrolidine for conversion of compound of **formula 3** to compound of **formula 4**. However, the yield obtained with use of secondary amines such as diethyl amine is poor.

PCT publication **WO 01/62722** (Equivalent of which is US 2002/0133032A1, Indian reference not available) discloses the method of preparing the compound of **formula 1** by reacting a compound of **formula 2** with dimethylthiocarbamoyl chloride and molar equivalents of sodium iodide in 2-butanaone to get compound of **formula 3**. The compound of **formula 3** is then reacted with a hydrolyzing agent such as sodium hydrosulfide to generate the sodium salt of **formula 4**, which can be alkylated *in-situ* with chlorofluoromethane to yield the compound of **formula 1** or alternately can be acidified to obtain the compound of **formula 4**, which can be isolated and converted to compound of **formula 1** by alkylation with chlorofluoromethane. This prior art publication teaches use of an alkoxide salt, a thioalkoxide salt or a hydrated sulphide salt for hydrolyzing the compound of **formula 3** to obtain the corresponding thiocarboxylic acid, the compound of **formula 4**. The use of sodium hydrosulphide hydrate or sodium thiomethoxide as hydrolyzing agent for conversion of carboxylic acid to carbothioic acid

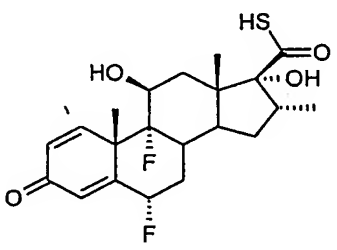
has been exemplified. However, sodium thiomethoxide is a corrosive and moisture sensitive reagent and use of sodium thiomethoxide would generate toxic methyl mercaptan during acidification and sodium hydrosulfide is unstable and converts to sodium thiosulfate and sodium carbonate upon storage. In the in-situ alkylation of sodium salt of compound of **formula 4**, the excess sodium hydrosulfide would react with the chlorofluoromethane generating highly toxic bis(fluoromethyl)sulfide, which can pose severe health hazards. Although isolation of thioic acid of **formula 4** can be performed (by treatment with an acid) to overcome the problem caused by excess sodium hydrosulfide, the sulfur will also precipitate in the acidification step, whose removal would be very difficult.

Some other shortcomings of this prior art method include (i) the time taken for the completion of alkylation reaction with chlorofluoromethane is very long, requiring about 26 hours. (ii) the amount of chlorofluoromethane required is in large molar excess, with almost 7.5 molar equivalents being used, and (iii) chlorofluoromethane being a gas would create handling difficulties.

Gordon H. Phillipps et al, **Journal of Medicinal Chemistry** 37, 3717-3729 (1994), disclose the method of preparing the compound of **formula 1** by treating a compound of **formula 6** with carbonyldiimidazole under nitrogen, followed by a reaction with hydrogen sulfide to give the thioic acid of **formula 7**, which is isolated and treated with propionyl chloride to give the compound of **formula 4.** This compound is then alkylated with bromofluoromethane under nitrogen to yield the compound of **formula 1** in 69.3% yield. This reference does not mention the preparation of compound of **formula 1** directly from the compound of **formula 3**.



6



7

In the process of the present invention an alkali metal carbonate is used as a hydrolyzing agent for conversion of a compound of **formula 3** to a compound of **formula 4** in contrast to prior art use of an alkoxide, a thioalkoxide or hydrated sulphide salt (as in WO 01/62722) or use of amines such as diethyl amine as in the '121 patent for this reaction.

OBJECT OF THE INVENTION

The object of the present invention is to provide a facile, efficient and economic process for the preparation of S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate.

In particular, the process of the present invention provides a simple and economical process wherein an alkali metal carbonate is used for conversion of a compound of **formula 3** to a compound of **formula 4**. Use of alkali metal carbonate provides improved yield of compound of **formula 4**.

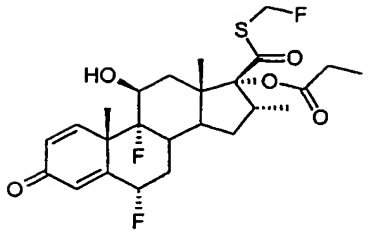
SUMMARY OF INVENTION

We have found a facile, efficient and economic process for the preparation of S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate (compound of **formula 1**) that provides an improved yield of the compound, using reagents that are easy to handle, utilizing a low reaction time and using the reagents in lesser molar amounts.

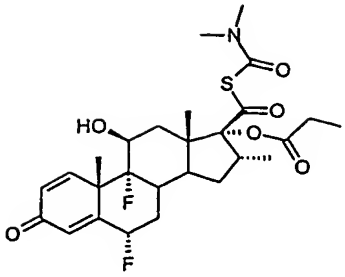
The present invention provides a process for the preparation of S-fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate, a compound of **formula 1**, comprising

(a) reacting the compound of **formula 3** with an alkali metal carbonate in an alkanol solvent to obtain the compound of **formula 4**;

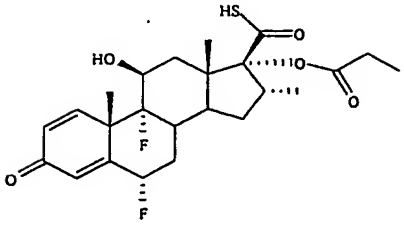
(b) reacting the compound of **formula 4** with bromofluoromethane to yield the compound of **formula 1**;



1



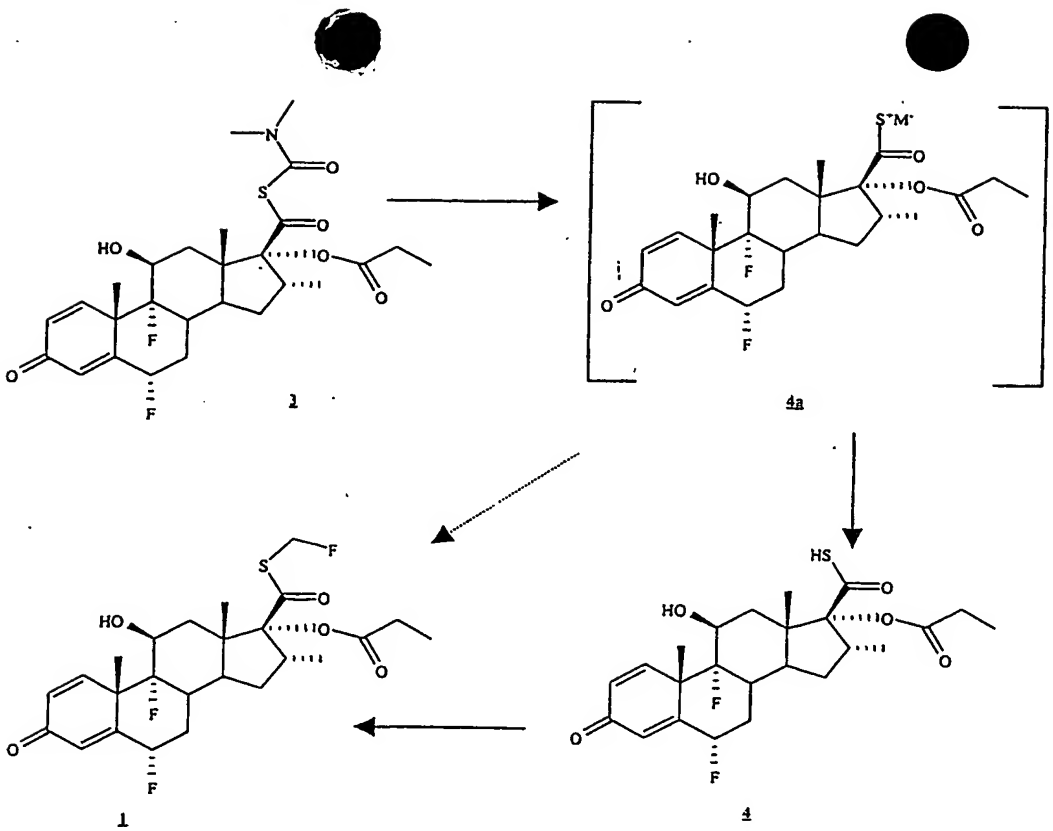
3



4

DETAILED DESCRIPTION OF THE INVENTION

In the process of the present invention the compound of **formula 3** is converted to a compound of **formula 4** by reacting with an hydrolyzing agent, which is an alkali metal carbonate to generate the alkali metal salt of compound of **formula 4**, viz., a compound of **formula 4a**, wherein M is the metal ion corresponding to the alkali metal carbonate used, such as K, Na or Li. The compound of **formula 4a** can be neutralized *in-situ* by treatment with an acid to obtain the compound of **formula 4**. The compound of **formula 4** is then reacted with bromofluoromethane to obtain the compound of **formula 1**. It is also possible to convert the compound of **formula 3** to the compound of **formula 1** directly i.e. without isolating the compound of **formula 4** by avoiding the reaction of compound of **formula 4a** with the acid, and directly reacting the compound of **formula 4a** generated in-situ with bromofluoromethane to obtain the compound of **formula 1** (See **Scheme 1**).



Scheme 1

The term "alkali metal carbonate", as used herein, refers to potassium carbonate, sodium carbonate, cesium carbonate and the like.

The term "acid", as used herein, refers to reagents capable of donating protons during the course of the reaction. Examples of acids include mineral acids such as HCl, HBr, HI, sulfuric acid, phosphoric acid and the like; organic acids such as acetic, formic, trifluoroacetic acid and the like; and sulfonic acids such as para-toluenesulfonic acid and the like.

Further in the process of the present invention for alkylating the compound of **formula 4**, bromofluoromethane, a liquid, which is easier to handle is used, as compared to chlorofluoromethane, a gas, which is used in the prior art process of WO 01/62722. The process of the present invention also utilizes lesser molar amounts of bromofluoromethane, as compared to the large molar amounts of chlorofluoromethane required in the prior art process. Also, the alkylation with bromofluoromethane requires shorter reaction time.

According to the process of the present invention, in step 'a' of the process, the reaction of compound of **formula 3** is carried out with an alkali metal carbonate in an alkanol solvent to obtain the compound of **formula 4**.

Examples of alkali metal carbonate that can be used include sodium carbonate, potassium carbonate, cesium carbonate and the like. The most preferred hydrolyzing agent is potassium carbonate.

In a preferred embodiment of the process of the present invention, the compound of **formula 3** is treated with potassium carbonate in methanol at ambient temperature for about 3 hour to about 10 hours. The reaction mixture is worked up by addition of water, followed by washing with an organic solvent such as toluene. The separated aqueous layer is acidified with an acid such as HCl acid to pH of about 1.5 to about 2 and the precipitated product is isolated.

In step 'b' of the process of the present invention, the compound of **formula 4** is alkylated with bromofluoromethane

The mole ratio of bromofluoromethane to the compound of **formula 4** may be in the range of about 1:1 to about 5:1. Preferably, the mole ratio of bromofluoromethane to the compound of **formula 4**, used in the process of the present invention, is 3:1.

In a preferred embodiment of the process of the present invention, the compound of **formula 3** is treated with potassium carbonate in methanol at ambient temperature for about 3 hour to about 10 hour. The reaction mixture is worked up by addition of water, followed by washing with an organic solvent such as toluene. The separated aqueous layer is acidified with an acid such as HCl acid to pH of about 1.5 to about 2 and the precipitated product is isolated to obtain a compound of **formula 4**. The compound of **formula 4** is reacted with bromofluoromethane in presence of potassium carbonate in acetone at about 0°C to about -5°C for a period of about 3 hours to about 10 hours. The reaction is quenched by addition of water and the precipitated product is isolated to obtain a compound of the **formula 1**.

It is also possible to prepare the compound of **formula 1** by the process of the present invention wherein the compound of **formula 3** is reacted with an alkali metal carbonate to obtain the compound of **formula 4a** which is not treated with an acid but is converted to compound of **formula 1** directly by reaction with bromofluoromethane.

The compound of **formula 1** may be purified by treatment with a solvent system comprising one or more organic solvents selected from alcohols, esters, ethers, ketones, amides, nitriles, aliphatic or aromatic hydrocarbons and mixtures thereof. The ratio of the organic solvent to the compound of **formula 1** is in the range of about 1:1 to about 50:1

The compound of **formula 3** can be prepared, for example, by reacting 6 α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α–(propionyloxy)-androsta-1,4-dien-17-β–carboxylic acid, a compound of **formula 2**, with N,N-dimethylthiocarbamoyl chloride in an inert aprotic solvent in the presence of an iodide catalyst and a base. In the prior art process of **WO 01/62722** the compound of formula 2 is reacted with N,N-dimethylthiocarbamoyl chloride in 2-butanone and sequentially treated with triethylamine, sodium iodide and water. However, the reaction mixture becomes unstirrable slurry after addition of sodium iodide and water. Whereas, in the process of the present invention it was observed that when the compound of formula 2 is reacted with N,N-dimethylthiocarbamoyl chloride in tetrahydrofuran and sequentially treated with triethylamine and catalytic tetrabutyl ammonium iodide the reaction mixture remains clear.

The base selected may be inorganic or organic. Examples of inorganic bases that may be used in the present invention include hydrides, hydroxides, carbonates, or fluorides of alkali or alkaline earth metals. The organic base may be selected from secondary or tertiary amines and quaternary ammonium bases which may be cyclic or acyclic, Preferably, the organic base is selected from hindered acyclic or cyclic tertiary amines and quaternary ammonium bases. In a preferred embodiment, an organic base is used. Particularly preferred organic base is triethylamine.

The iodide catalyst may be an iodide salt selected from alkali metal iodides, alkaline earth metal iodides and quaternary ammonium iodides, the preferred catalyst being quaternary ammonium iodides, most preferably tetrabutylammonium iodide. The mole ratio of the catalyst to 6α,9α-difluoro-11β-hydroxy-16 α-methyl-3-oxo-17α–(propionyloxy)androsta-1,4-dien-17β–carboxylic acid, the compound of **formula 2** that may be used in the process of the present invention lies in the range of about 0.01:1 to about 0.5:1, preferably 0.1:1.

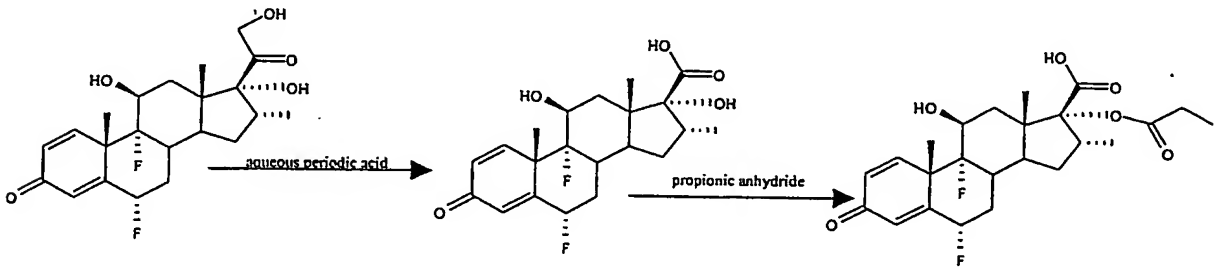
The reaction of a compound of **formula 2** with N,N-dimethylthiocarbamoyl chloride may be carried out in an inert aprotic solvent such as aliphatic or aromatic hydrocarbons, ethers, esters, nitriles and amides, or mixtures thereof. In preferred embodiments of the present invention ethers are used as the solvents. The ethers that are used are, cyclic or acyclic such as tetrahydrofuran, dioxane, diethyl ether, diisopropyl ether, tert-butyl methyl ether and the like, and mixtures thereof; more preferably tetrahydrofuran is used as the solvent.

The reaction of a compound of **formula 2** with N,N-dimethylthiocarbamoyl chloride may be carried out at temperature ranging from -10° C to 100° C, preferably from about 0° C to 25° C.

Preferably the compound of **formula 3** is prepared by treating the compound of **formula 2** with N,N-dimethylthiocarbamoyl chloride in tetrahydrofuran, in the presence of triethylamine and tetrabutyl ammonium iodide at room temperature, followed by cooling to 10 -15°C. The reaction mixture is warmed to ambient temperature and stirred for 2-8 hours, preferably for 4 hours. At the end of the reaction, the reaction mixture is treated sequentially with a polar aprotic solvent and water. This polar aprotic solvent may be selected from dimethylformamide, dimethylacetamide and dimethyl sulfoxide and the like; the preferred solvent being dimethylacetamide. The mixture is then cooled to 0° C, stirred and the compound of **formula 3** is isolated.

The compound of **formula 2**, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carboxylic acid, may be prepared in conventional manner e.g. by oxidation of 6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3,20-dione-21-hydroxy-androsta-1,4-diene i.e. flumethasone, followed by reaction with propionyl chloride or propionyl anhydride. The oxidation reaction may be carried out with a suitable oxidizing agent such as periodic acid.

Given below is the schematic representation of a preferred process by which a compound of the **formula 2** may be prepared.



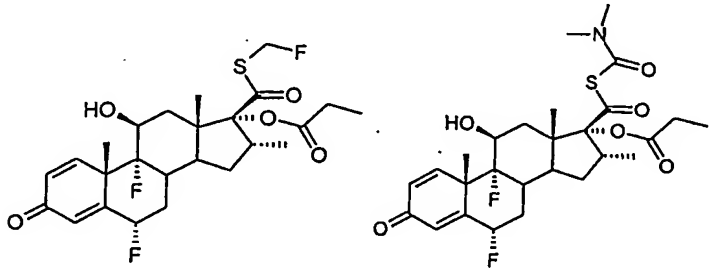
2

The present invention is further defined by the following:

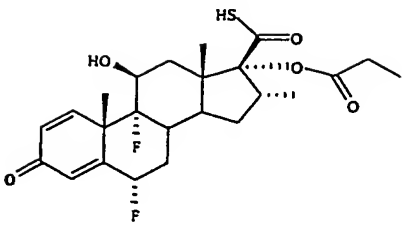
A] A process for the preparation of S-fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate, a compound of **formula 1**, comprising

(a) reacting the compound of **formula 3** with an alkali metal carbonate in an alkanol solvent to obtain the compound of **formula 4**;

(b) reacting the compound of **formula 4** with bromofluoromethane to yield the compound of **formula 1**;



1 3



4

B] The process as defined in 'A' above, wherein the alkali metal carbonate is potrassium carbonate.

C] The process as defined in 'A' above, wherein the alkanol is methanol.

D] The process as defined in 'A' above, wherein the mole ratio of bromofluoromethane to the compound of **formula 4** is 3:1.

E] The process as defined in 'A' above, wherein the compound of **formula 3** is prepared by reacting 6 α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α–(propionyloxy) androsta-1,4-dien-17β–carboxylic acid, a compound of **formula 2**, with N,N-dimethylthiocarbamoyl chloride in an inert aprotic solvent in the presence of an iodide catalyst and a base.

F] The process as defined in 'E' above, wherein the inert aprotic solvent is an ether.

G] The process as defined in 'F' above, wherein the ether solvent is tetrahydrofuran.

H] The process as defined in 'E' above, wherein the iodide catalyst is tetrabutylammonium iodide.

I] The process as defined in 'H' above, wherein the mole ratio of the catalyst to the compound of **formula 2** is 0.1:1.

J] The process as defined in 'E' above, wherein the base is an organic base.

K] The process as defined in 'J' above, wherein the organic base is triethylamine.

The invention is illustrated but not restricted by the description in the following examples.

EXAMPLE

Example 1: Preparation of 6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid

A solution of periodic acid (83g, 0.365 mole) in water (200ml) is prepared by heating to 50-55° C and cooling to 30-35° C. This solution is added dropwise to a stirred suspension of flumethasone (100g, 0.244 mole) in tetrahydrofuran (400ml) at 0-5° C. After completion of addition the mixture is stirred for further 2 hrs. at 0-5° C and thereafter quenched by addition of water (600ml) while maintaining temperature at 5-15 ° C, then cooled to 0-5° C and filtered. The product 6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid is washed with water (~2.0 ltr), and dried at 45-50° C. Yield 92.0g (95.3%, purity 99.55%).

Example 2: Preparation of 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(propionyloxy)-androsta-1,4-diene-17β-carboxylic acid, a compound of formula 2

To suspension of 6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (80g, 0.202mole) in acetone (400ml) at 10-15° C is added sequentially triethylamine (85ml, 0.606mole) and propionic anhydride (78ml, 0.606mole). After stirring for 4 hrs. at 25-30° C, dimethylamine (42ml, 0.404mole) is added dropwise at 10-15° C and then stirred at ambient temperature for 1 hr. Thereafter the reaction mixture is acidified to pH 1.0 –1.5 at 0-5° C. The precipitated product is filtered, washed with water, and dried at 4-45° C, until water content is below 5%. Yield 90g on dry basis (98.6%, purity >99.5%)

Example 3: Preparation of 17β-[(N,N-dimethylcarbamoyl)thio]carbonyl-6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-propionyloxy-3-oxoandrosta-1,4-diene, a compound of formula 3

A solution of 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(propionyloxy)androsta-1,4-diene-17β-carboxylic acid, (50.0 g, 110 mmol) and N,N-dimethylthiocarbamoyl chloride (27.4 g, 222 mmol) in tetrahydrofuran (250 ml) at room temperature is cooled to 10 to 15^{0}C. It is sequentially treated with triethylamine (24.9 g, 244 mmol) and tetrabutylammonium iodide (4.1 g, 11 mmol) at 10-15^0 C. The reaction mixture is warmed to ambient temperature, stirred for 4 hrs and then treated sequentially with dimethylacetamide (150 ml) and water (1.0 lit). The resultant mixture is cooled to 0^0 C, stirred for 2 hours, and the product is filtered. The solid obtained is washed with water (230 ml) and dried at 55^0 C for 4.0 hours to provide 57.0 g (96.0% yield, purity >98.5%) of 17β-[(N,N-dimethylcarbamoyl)thio]carbonyl-6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-propionyloxy-3-oxoandrosta-1,4-diene.

Example 4: Preparation of 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioic acid, a compound of formula 4

A suspension of 17β-[(N,N-dimethylcarbamoyl)thio]carbonyl-6α,9α-difluoro-11β-hydroxy- 16α-methyl-17α-propionyloxy-3-oxoandrosta-1,4-diene (20 g, 0.037 mol.) and potassium carbonate (10.23 g, 0.074 mol.) in methanol (100 ml) is stirred at ambient temperature for 5 hrs under a blanket of nitrogen. Thereafter, water (100 ml) is added to the reaction mixture and the resultant clear solution is extracted with toluene (60 ml). The aqueous layer containing the product is charcoalized (2 g charcoal) at ambient temperature and then acidified with 2N HCl until pH is 1.5 to 2.0. The precipitated product is filtered, washed with water, and dried at 50-60° C to obtain 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α–propionyloxy-3-oxo-androsta -1,4-diene-17β–carbothioic acid (5) (yield 17.3 g, moisture content 3.3%, 96.33% on dry basis).

Example 5: Preparation of S-fluoromethyl 6 α,9 α-difluoro-11β-hydroxy-16 α-methyl-17α–propionyloxy-3-oxoandrosta-1,4-diene-17β–carbothioate, compound of formula 1

A stirred mixture of 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α–propionyloxy-3-oxo-androsta-1,4-diene-17β–carbothioic acid (5) (4 g, 0.0085 mol)) and anhydrous potassium carbonate (0.82 g, 0.0059 mol.) in acetone (20ml) under a blanket of nitrogen is cooled to 0 to –5°C and bromofluoromethane (1.05g, 0.009 mol.) is added. The mixture is then stirred at 0 to –5°C for further 5 hrs and then quenched with water (20 ml). The precipitated product is filtered, washed with water (8 ml), and dried to obtain crude product (yield: 3.625 g, moisture content 0.36%, 84. 8%, purity 98.11%)

Example 6: Purification of compound of formula 1

The crude fluticasone obtained as above is dissolved in 68 ml 1-butanol at 117-120°C to get a clear solution (which may be optionally charcoalized and filtered hot), and then gradually cooled to ambient temperature for crystallization. The crystallized product is filtered. washed with 1-butanol (4ml). Dried at 55-60°C to obtain pure fluticasone propionate (Yield 3.0 g, purity 99.24%)

Dated this 10th day of April 2003.

DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LIMITED